

**REMARKS/ARGUMENTS**

With entry of the foregoing amendment, claims 47-55, 57, 59-60, 63-67, 69, 73-79, 83-84, 86-89, 91-92, 97-99, 101-105, 107, 109-114, 118, 120, 122, and 125-135 are pending in the application. Claims 1-46, 56, 58, 61, 62, 68, 70-72, 80-82, 85, 90, 93-96, 100, 106, 108, 115-117, 119, 121, and 123-124 are cancelled. Claims 47-55, 57, 59, 60, 63, 69, 73-79, 83-84, 86-87, 97-98, and 105 are withdrawn. Claims 64-67, 88, 89, 91, 92, 99, 101-105, 107, 109-114, 118, 120, 122 and 125-131 are under consideration. Claims 47 and 64 are currently amended to advance prosecution. Support for the amendments can be found throughout the specification including at page 28, lines 42-44. Claims 130 and 131 were amended for purposes of clarity. Claims 132-135 are newly added. Support for claims 132-135 can be found at least at page 19, lines 11-12 and 31, page 20 at line 6, page 28, lines 1-7 and page 30, line 6 through page 31. No new matter is added by the amendments. Entry of the amendments and reconsideration of the claims is respectfully requested.

Applicants thank the Examiner for the courtesies extended in our telephone conversation on Friday, August 12, 2011 and Monday August 15, 2011.

**Priority Claim**

Applicants note that no filing receipt was ever received in the current application. Applicants filed a Request for a Filing Receipt on August 17, 2011. Upon investigation applicants noted that the priority claim to the U.S. Provisional Application No. 60/465,807 was mistakenly listed as a foreign priority claim on the Declaration filed with the application. The specification was properly amended to add the correct priority claim on February 20, 2009 and Applicants believed that the priority claim would be corrected. We are filing a replacement Declaration with the proper priority claim and a replacement Application Data Sheet with the proper claim of priority. We respectfully request that the priority to the indicated U.S. Provisional Application be accorded the application. Because the filing receipt has not been received, Applicants believe the priority claim should be corrected by the Office without need for a Petition to Accept an Unintentionally Delayed Priority Claim.

**Claim Objection**

The Examiner objected to claims 64-67, 88-89, 91-92, 99, 101-104, 107, 109-114, 118, 120,

122, and 125-131 as drawn in part to non-elected subject matter. The elected subject matter has been found allowable and the non-elected subject matter found not allowable has been deleted from the claims. Applicants note that once the elected subject matter is found allowable the non-elected subject matter can be searched. Applicants respectfully request the Examiner to broaden the search.

**Rejections under 35 U.S.C. §112, second paragraph**

Claims 64-66, 91, 99, 101-104, 107, 109-114, 118, 120, 122 and 125-131 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite. The Examiner notes that the rejection was necessitated by the amendment to claim 64 which recites variables not recited in the claim. With entry of the foregoing amendments, this amendment is cancelled and the compound XAC-Bodipy 630/650 X has been specifically deleted from the claim. Applicants respectfully request that the rejection be withdrawn.

**Rejection under 35 U.S.C. §103**

Claims 64-67, 88-89, 91, 99, 101-104, 107, 109-114, 118, 120, 122, and 125-131 are rejected under 35 U.S.C. §103(a) as unpatentable over the combination of Boring, Burchard, Buschmann, Jacobson, Heefner, Sauer and Cherif. The Examiner contends that the GPCR ligand XAC has been conjugated to different molecules including fluorescent dyes and points to Boring (XAC conjugated to NBD), Jacobson- Biochem Pharm (XAC conjugated to fluorescein), Heefner (XAC conjugated to monochlorofluorescein or sulfofluorescein). Jacobson-FEBS also teaches conjugating XAC to other molecules including lipids and peptides, and diamino-, thiol-, aldehyde and halogen substituted derivatives of XAC. None of these references teaches that XAC can be conjugated to Bodipy 630/650 X, or any other 4,4-difluoro-4-bora-3a,4a-diaz-s-indacene dye. To overcome this deficiency in the *prima facie* case, the Examiner notes that Bodipy has been conjugated to many different molecules and points to Sauer (Bodipy conjugated to dUTP), Cherif (Bodipy conjugated to DNA), Buschard (Bodipy conjugated to DNA) and Buschmann (Bodipy conjugated to biotin). The Examiner then argues that one of skill in the art would have a reasonable expectation of success in conjugating XAC to Bodipy to generate a compound used in biological experiments, because one skilled in the art would have realized the interchangeability of the fluorescent dyes.

Essentially the Examiner is arguing that the claims are obvious because they represent a simple

substitution of one known element (a known fluorophore) for another to yield predictable results. The problem with the Examiner's assertion is that it ignores the unexpected results reported in the application and claimed in at least claim 118. A *prima facie* case of obviousness may be rebutted by proof that the claimed compounds possess unexpectedly superior properties. See MPEP 2144.09 (VII). Based on the cited references, one of skill in the art would predict that the compound XAC-Bodipy would behave similarly to XAC-fluorescein or the other XAC-fluorescent tagged molecules described by Boring, Jacobson and Heefner. Thus, one would predict using the Examiner's reasoning that the compounds claimed herein (e.g., XAC-Bodipy 630/650-X) would fluoresce equivalently when the ligand was bound to the GPCR and when unbound in the media.

Claim 118, the specification at least at page 45, lines 16-20, and page 32, lines 1-4 ("With ligands showing low background fluorescence it is not necessary to remove unbound ligand by washing before performing confocal microscopy. It is therefore possible to measure fluorescence with time, in both time and concentration dependent manner.") and the declaration under 1.132 submitted in response to the November 27, 2009 Office action (see second full paragraph on page 7) highlight that these compounds are distinct and possess the unexpectedly superior property of having low background fluorescence when unbound in the media and increased fluorescence when bound to the GPCR. GPCRs, unlike most other cellular receptors, have ligand binding sites located deep within transmembrane regions and the ligands (and any molecule attached thereto) are brought into close proximity with the membrane when the ligand is bound to the GPCR. Without being bound by theory, the inventors have subsequently reported that the Bodipy fluorophore may be in close proximity to the non-polar membrane environment or may embed into the membrane upon interaction of the attached GPCR ligand with its receptor. Baker et al. 2010 British J Pharmacology 159:772-785. When the Bodipy fluorophore is in proximity to the membrane the fluorescence intensity increases (it becomes brighter) such that the bound compound can be detected over and above any unbound ligand (i.e. reported as low background fluorescence) and without any need for washing the unbound compound away. This result (i.e. low background fluorescence in aqueous media) is not predicted by any of the cited references and the unexpected advance allows for real time cellular assays. The prior art compounds do not display a similar phenomenon and do not allow for real time cellular assays. Thus, Applicants respectfully request that the rejection be withdrawn.

**Rejection Based on Non-statutory Obviousness-type Double Patenting**

Claims 64-67, 88-89, 91-92, 99, 101-104, 107, 109-114, 118, 120, 122 and 125-131 remain provisionally rejected on the ground of non-statutory obviousness-type double patenting over co-pending Application No. 11/576,035. Because this rejection is merely provisional in nature, Applicants respectfully request that the rejection be held in abeyance until such time as allowable subject matter is identified.

**Conclusion**

In view of the amendments and remarks above, Applicants respectfully request reconsideration on the merits and withdrawal of the rejections. Applicants respectfully submit that pending claims 64-67, 88, 89, 91, 92, 99, 101-105, 107, 109-114, 118, 120, 122 and 125-135 are allowable and respectfully request allowance of the claims.

The Examiner is encouraged to contact the undersigned if any clarification regarding this response is required.

Respectfully submitted,

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